The involvement of the transcription factor ATF7 in the regulation of metabolism

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論文の要旨
Abstract of thesis

Purpose: The growing epidemic of obesity poses serious health risks due to the development of obesity-associated diseases including type 2 diabetes, hypertension, heart diseases, and cancer. When energy intake consistently exceeds energy expenditure, excess calories are stored as triglycerides in white adipose tissue. By contrast, brown adipose tissue (BAT) and beige adipocytes are responsible for the dissipation of energy as heat by adaptive thermogenesis. The activating transcription factor (ATF)2 family of transcription factors regulates a variety of metabolic processes, including adipogenesis and adaptive thermogenesis. ATF7 is a member of the ATF2 family, and mediates epigenetic changes induced by environmental stresses, such as social isolation and pathogen infection. However, the metabolic role of ATF7 remains unknown. Assisted reproductive technologies, including in vitro fertilization (IVF), are now frequently used, and increasing evidence indicates that IVF causes gene expression changes in children and adolescents that increase the risk of metabolic diseases. Although such gene expression changes have been thought to be due to the IVF-induced epigenetic changes, its mechanism remains elusive. The applicant tried to investigate the role of ATF7 in regulation of metabolism and its function in the IVF-induced gene expression change.

Materials and method: To explore the role of ATF7 in metabolism, the applicant measured a series of metabolic parameters of *Atf7* deficient (*Atf7*-/-) and wild type (*WT*) mice, including body weight, insulin and glucose tolerance, energy expenditure, plasma glucose, triglycerides, and cholesterol concentrations, serum insulin and resistin levels. The histology analysis was performed to examine the cell morphology of adipose tissues. Gene expression changes

were detected by RT-PCR and microarray analysis. Protein expression and phosphorylation level were examined by western blotting. In vitro differentiation was implemented for investigation of the role of ATF7 in adipogenesis. Bioinformatics methods were applied to analyze the gene expression pattern in liver.

Result: *Atf7-/-* mice exhibited lower body weight and resisted diet-induced obesity. Serum triglycerides, resistin, and adipose tissue mass were all significantly lower in ATF7-deficient mice. Fasting glucose levels and glucose tolerance were unaltered, but systemic insulin sensitivity was increased by ablation of ATF7. Indirect calorimetry revealed that oxygen consumption by *Atf7-/-* mice was comparable to that of *WT* littermates on a standard chow diet, but increased energy expenditure was observed in *Atf7-/-* mice on a high-fat diet. The thermogenic genes, including Ucp1 and Ppargc1a, exhibited the higher expression levels in iWAT of *ATF7-/-* mice and the *UCP1* expression level was higher in BAT of *Atf7-/-* mice after cold exposure. Adipogenesis was impaired by ablation of ATF7. In contrast, overexpression of ATF7 in C3H10T1/2 cells promoted the process of adipogenesis. The applicant also found that IVF up-regulated the expression of 688 genes in the liver of 4-week-old *WT* mice, whereas 87% of these were not changed by IVF in *Atf7-/-* mice. The genes, which are involved in metabolism, such as pyrimidine and purine metabolism, were up-regulated in *WT* mice but not in *Atf7-/-* mice. Of the genes whose expression was up-regulated by IVF in *WT* mice, 37% were also up-regulated by a loss of ATF7.

Conclusion: These results showed that the ablation of ATF7 in mice could improve the resistance to diet-induced obesity and insulin sensitivity. *Atf7-/-* mice fed a HFD showed higher energy expenditure during both light and dark phases, implying that ATF7 may contribute to the regulation of adaptive thermogenesis. The up-regulated thermogenic genes in inguinal WAT of *Atf7-/-* mice and cold exposure-induced phosphorylation of ATF7 in BAT further confirm that ATF7 functions as transcriptional repressor in the thermogenic gene program. However, in vitro adipocyte differentiation demonstrated that ATF7 is required for adipogenesis. These data indicate that ATF7 controls the energy balance by regulation of adipocytes development and thermogenesis. In addition, our study also shown that ATF7 is a key factor in establishing the memory of IVF effects on metabolic pathways, such as pyrimidine and purine metabolism and terpenoid backbone biosynthesis.

審査の要旨
Abstract of assessment result

【批評 Review】

The applicant identified that ATF7 controls the energy balance by regulation of adipocytes development and thermogenesis. In addition, ATF7 is a key factor in establishing the memory of IVF effects on metabolic pathways, such as pyrimidine and purine metabolism and terpenoid backbone biosynthesis. These observations may open new understanding about epigenetic regulation of ATF7.

【最終試験の結果 Result】

The final examination committee conducted a meeting as a final examination on 14 September, 2017. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

【結論 Conclusion】

Therefore, the final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Human Biology.